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Spindle cell carcinoma of the esophagus

A multicenter analysis in comparison with typical squamous cell carcinoma

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Abstract

This study conducted a retrospective multicenter analysis to investigate the clinicopathological features, optimal therapeutic strategy, and prognosis of spindle cell carcinoma (SpCC) of the esophagus.

A total of 71 patients with esophageal SpCC from 3 large cancer centers in China were systematically analyzed. All patients received curative resection, 13 patients received adjuvant radiotherapy and 15 patients received adjuvant combination chemotherapy. Additionally, a total of 1852 patients with typical esophageal SCC (SCC) were selected as controls in this study.

SpCC mostly presented as a polypoid appearance (66.2%), and the surrounding mucosa showed high-grade hyperplasia or superficial SCC in 31 cases (43.7%). Two patients even had extensive carcinoma in situ that spread to the resection margins. Patients in the SpCC group were more likely to present with stage I lesions compared with those in the typical SCC group (33.8% vs 8.0%, $P<0.001$). Although the percentage of T1/2 lesions was higher in the SpCC group than in the typical SCC group (67.6% vs 29.7%, $P<0.001$), both groups had similar rates of locoregional lymphatic metastases (45.1% vs 48.4%, $P=0.578$). The median survival time and 5-year overall survival of the SpCC group was 43 months and 44.8%, respectively, higher than 37.5 months and 38.3%, respectively, for the typical SCC group ($P=0.044$). In univariate analysis, the macroscopical type and pathological T, N, and TNM stages had a statistically significant impact on the prognosis of SpCC after curative resection. However, only the TNM stage (hazard ratio, 2.708; 95% confidence interval, 1.786–4.105, $P<0.001$) was identified as an independent prognostic factor in multivariate analysis. The 5-year OS of SpCC in stages I (79.8%) and II (39.7%) were significantly longer than that of stages III/IV (16.2%) ($P<0.001$ and $P=0.012$). As those SpCC cases that received chemoradiotherapy were in more advanced stages, their prognosis was still worse than SpCC patients who did not receive chemoradiotherapy even after such treatment ($P=0.042$, 0.010, respectively).

SpCC shows a highly aggressive tendency of lymphatic spread, although it does not tend to infiltrate deeply into the esophageal wall. Compared with typical SCC that also underwent esophagectomy with extended lymphadenectomy, SpCC may achieve a better survival rate. Further investigation is warranted to examine the effect of postoperative chemoradiotherapy on the prognosis of SpCC.

Abbreviations: MST = median survival time, OS = overall survival, SCC = squamous cell carcinoma, SpCC = spindle cell carcinoma.

Keywords: carcinosarcoma, esophagus, sarcomatoid carcinoma, spindle cell carcinoma, squamous cell carcinoma

1. Introduction

Spindle cell carcinoma (SpCC) consisting of variable proportions of a malignant spindle cell component and a carcinomatous component is a rare subtype of esophageal tumor and has been the focus of a great deal of controversies in the past years.[1–3] Although SpCC is biphasic in cellular pleomorphism, it is now believed to be of monoclonal epithelial origin, with a sarcomatoid differentiation.[1–7] However, the heterogeneous morphological structure of SpCC has presented significant diagnostic challenges

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and led to a confounding list of names, including carcinosarcoma, sarcomatoid carcinoma, pseudosarcoma, polypoid carcinoma, and spindle cell carcinoma.[2,8] Characteristically, SpCC presents as a bulky pedunculated mass with a spindle cell component in the stroma and a squamous cell component on the surface, and the latter component may be invasive carcinoma, carcinoma in situ, or dysplasia.[2,9,10] Therefore, the biopsy samples taken in insufficient size and depth might miss one of the cellular components and lead to a misdiagnosis.[1]

Because of the rarity of SpCC, previous studies with single cases or small series have failed to achieve a consensus on the treatment modalities with respect to their efficacy.[9–13] Surgery was the main treatment in previous studies, but factors influencing the long-term prognosis of SpCC after surgery have seldom been identified.[9,11,12,14] In addition, because of incomplete data, no robust conclusion could be drawn about whether radiotherapy and chemotherapy could help improve the control of SpCC.[11,14,15]

Therefore, in this study, clinicopathological data of 71 cases with esophageal SpCC were retrospectively collected from 3 large cancer centers in China, and a comprehensive analysis was conducted to elucidate the clinicopathological features, optimal therapeutic strategy, and prognosis of this rare tumor. The overall survival (OS) for SpCC and conventional squamous cell carcinoma (SCC) were also compared based on the primary tumor stage and modality of treatment. This study is perhaps the largest series of esophageal SpCC from China to date.

2. Patients and methods

2.1. Patient eligibility and evaluation

This retrospective study included 71 patients with previously untreated esophageal SpCC who presented at the Hunan Cancer Hospital, Xiangya Hospital, and Cancer Hospital, Chinese Academy of Medical Sciences, between 1998 and 2012, accounting for 0.63% of all primary esophageal tumors treated in the same period. Medical records of these patients were comprehensively reviewed. Additionally, a total of 1852 patients with typical esophageal SCC, who received curative esophagectomy during the same period in the Hunan Cancer Hospital, were selected as controls in this study. The study was approved by the ethics committee of the Hunan Cancer Hospital.

According to the World Health Organization classification criteria, all diagnoses of SpCCs were reconfirmed on the basis of the morphological features and immunophenotypic staining by 2 experienced pathologists. Immunohistochemical staining was performed using a specific monocolonal antibody against Smooth Muscle Antigen (undiluted, Kit-0006, Maxim), Vimentin (undiluted, Kit-0019, Maxim), Epithelial Membrane Antigen (undiluted, Kit-0011, Maxim), and Cytokeratin (Pan) (undiluted, Kit-0009, Maxim) on formalin-fixed paraffin-embedded human samples, according to the manufacturer's protocols.

2.2. Treatment

Overall, curative esophagectomy with the stomach as an esophageal substitute was carried out in 70 patients, and mid and inferior mediastinal and upper abdominal lymph nodes were routinely dissected. One patient with a superficial lesion received endoscopic membrane resection. After operation, adjuvant radiotherapy using 6-MV photons was delivered in 13 patients (18.3%, 13/71), which was begun 3 to 4 weeks after surgery with a median dose of 60.0 Gy (range, 58–64 Gy) at 1.8 to 2.0 Gy per fraction. Adjuvant combination chemotherapy based on platinum regimens (cisplatin [75 mg/m^2] or carboplatin [AUC 4–6] plus Taxol [135–175 mg/m^2], Nedaplatin [80–100 mg/m^2] plus Taxol [135–175 mg/m^2], etc.) was given in 15 patients 3 to 4 weeks after surgery, with a median course of 3 cycles (21 days per cycle, 1–5 cycles). Among them, 4 patients were treated with concurrent chemoradiotherapy which started at the same time without modification about the regimens and dosages.

2.3. Statistical analysis

The follow-up information was collected via telephone call, letters, e-mails, or regular outpatient follow-up. The OS was calculated as the number of months from the date of initial treatment to the date of death or last follow-up. The primary endpoint of the analysis was 5-year OS. Patients lost to follow-up or alive at the end of the study were considered censored.

The SPSS version 15.0 software (SPSS Inc., IL) was used for all statistical analysis. Differences in clinicopathological features between groups were assessed by the chi-square (χ^2) test or t test. Kaplan–Meier survival analyses were used to calculate the OS and median survival time (MST), and the statistical significance between groups were determined by the log-rank analysis. Variables that were significant on univariate analysis were included into the Cox proportional hazard regression model to determine the independent prognostic factors. A 2-sided probability value (P value) of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Patient demographics and clinicopathological characteristics of esophageal SpCC and typical SCC are summarized in Table 1. The SpCC group consisted predominantly of males (male: female = 4.9:1) with a mean age of 58.04 ± 9.66 years old (range, 39–80 years old); about 60% of the patients were <60 years in age. The history of exposure to cigarette and alcohol consumption was recorded in 44 patients (62%) and 35 patients (49.3%), respectively. A family history of esophageal carcinoma was observed in 12 patients (16.9%). Progressive dysphagia was the most principal manifestation (87.3%) in the initial diagnosis, and weight loss was recorded in 16 patients (22.5%). The duration of symptoms was shorter than 3 months in most of the patients (58 cases, 81.7%). The primary lesions were most often located in the middle and lower thoracic esophagus (58 cases, 81.7%). The median tumor length was 5.0 cm (range, 2.0–18.0 cm). Of the 71 cases who underwent preoperative esophagoscopy, only 10 cases (14.1%) were diagnosed with SpCC or sarcoma, whereas the others were mistakenly diagnosed as typical SCC or false negative. Endoscopic ultrasonography was performed in 24 cases, which indicated a hypoechoic and heterogeneous mass principally located in the submucosal and muscular layer, with irregular and unclear margins.

3.2. Pathological analysis

According to the barium esophagography and surgical specimens, 47 cases were classified as polypoid type, showing irregular exophytic polypoid tumors of different sizes, ranging from the smallest of $2.0 \times 1.0 \times 1.0$ cm^3 to the largest of $13.0 \times 7.0 \times 6.0$ cm^3. The intraluminal tumor was often covered with superficial

Table 1

Clinical characteristics and staging for SpCC patients (n = 71) and typical SCC (n = 1852).

	No. of SpCC (%)	No. of typical SCC (%)	*P*
Age, y			
Mean ± SD	58.04 ± 9.66	59.22 ± 10.195	0.126
Gender			
Male	59 (83.1%)	1471 (79.4%)	
Female	12 (16.9%)	381 (20.6%)	0.452
Tumor location			
Upper-third esophagus	13 (18.3%)	325 (17.5%)	
Mid-third esophagus	38 (53.5%)	907 (49.0%)	
Lower third esophagus	20 (28.2%)	620 (33.5%)	0.641
Pathological T stage			
T1	35 (49.3%)	141 (7.6%)	
T2	13 (18.3%)	409 (22.1%)	
T3	13 (18.3%)	1041 (56.2%)	
T4	10 (14.1%)	261 (14.1%)	<0.001
Macroscopical type			
Polypoid type	47 (66.2%)	153 (8.3%)	
Infiltrative type	24 (33.8%)	1699 (91.7%)	<0.001
Pathological N stage			
N-	39 (54.9%)	955 (51.6%)	
N+	32 (45.1%)	897 (48.4%)	0.578
Pathological TNM stage			
Stage I	24 (33.8%)	149 (8.0%)	
Stage II	20 (28.2%)	853 (46.1%)	
Stage III/IV	27 (38.0%)	850 (45.9%)	<0.001

SCC = squamous cell carcinoma, SpCC = spindle cell carcinoma of the esophagus, TNM = tumor-node-metastasis.

ulceration on the surface and had a pedicle connected to the esophageal wall. A total of 24 cases were classified as infiltrative type, showing extensive intramural spread or medullary, fungating tumors with deep ulceration and raised everted edges. The gross appearances of the latter type of SpCC were comparable to those of typical SCC. In further analysis, the invasion depth of polypoid tumors was limited in mucosa/submucosa (T1) or muscularis propria (T2) in 43 cases (91.5%), whereas in 24 infiltrative tumors, 19 cases (79.2%) had the adventitia (T3) or adjacent pleura and diaphragm (T4a) involved ($P < 0.001$). Therefore, the infiltrative tumors tended to infiltrate more deeply into the esophageal wall.

Microscopically, a carcinomatous component was admixed with a variable proportion of a malignant spindle cell component. Most of the carcinomatous component consisted of malignant squamous cell (67 cases) (Fig. 1); however, a few of them were adenosquamous carcinoma (2 cases, middle and lower third of the thoracic esophagus), adenocarcinoma (1 case, lower third), and neuroendocrine carcinoma (1 case, mid third). The spindle cell component was indistinguishable from a sarcoma and may contain leiomyosarcoma, rhabdomyosarcoma, malignant fibrous histiocytoma, chondrosarcoma, osteosarcoma, or other types of mesenchymal differentiation. The background mucosa adjacent to the pedicle showed moderate-to-severe atypical hyperplasia or superficial SCC in 31 cases (43.7%). Two of these patients had extensive carcinoma in situ in esophageal mucosa that spread even to the resection margins. Immunohistochemical staining was performed in 54 cases, showing vimentin (40/44), smooth muscle antigen (7/11), actin (Pan) (7/13), cytokeratin (Pan) (46/52), and epithelial membrane antigen (16/20) positive to a certain degree (Fig. 2).

The pathological TNM stage was classified according to the seventh edition of the AJCC (American Joint Committee on Cancer) Cancer Staging system for esophageal carcinoma (Table 1). Of all SpCC patients, 35 cases (35/71, 49.3%) had lesions in pathological stage T1 and 13 cases had lymph node metastases (13/35, 37.1%). But of the 1852 cases with typical SCC, only 141 cases (141/1852, 7.6%) were in stage T1 ($P < 0.001$) and 41 cases (41/141, 29.1%) had lymph node metastasis ($P = 0.354$). In the stage T2 group, 13 cases in the SpCC group had lesions in pathological stage T2 and 7 cases had lymph node metastases (7/13, 53.8%), which was not significantly different from that of 40% in typical SCC cases (163/409) ($P = 0.311$). Taken together, although the percentage of stage T1/2 lesions was higher in the SpCC group than in the typical SCC group (48/71, 67.6% vs 550/1852, 29.7%, $P < 0.001$), both groups had similar rates of locoregional lymph node metastases (32/71, 45.1% vs 897/1852, 48.4%, $P = 0.578$). However, patients in the SpCC group were more likely to present with stage I lesions compared with those in the typical SCC group (24/71, 33.8% vs 149/1852, 8.0%, $P < 0.001$).

3.3. Prognostic factor analysis

Overall, 64 patients (90.1%) achieved radical resection, and the other 7 cases received palliative resection; 12 patients (16.9%) had postoperative complications occurring within 1 month after operation, including anastomotic leakage (4), incisional infection (3), pyothorax (2), chylothorax (1), pulmonary artery embolism (1), and aspiration pneumonitis (1). Two patients died of sepsis caused by anastomotic leakage and respiratory failure, with the perioperative mortality of 2.8% (2/71).

Till October 2015, the median follow-up of the whole group was 49 months, with the range of 1 to 193 months. At the end of the follow-up, 36 patients died of tumor recurrence, 2 died of postoperative complications, 1 died of comorbidity, and 2 died of unknown reasons; 26 patients were alive without tumor recurrence and 4 cases were lost to follow-up.

The clinicopathological features and prognosis of SpCC are analyzed in Table 2. The MST and 5-year OS were 129.0 months and 51.7%, respectively, in patients with polypoid tumors, and 14.0 months and 30.6%, respectively, in patients with infiltrative tumors (Fig. 3, $P = 0.001$). The MST and 5-year OS of patients with pathological T1/2 were 86.0 months and 51.8%, respectively, and with pathological T3/4 were 13.0 months and 29.6%, respectively (Fig. 4, $P = 0.002$). The survival of patients without locoregional lymphatic metastasis was longer than that with lymphatic metastasis (Fig. 5, $P < 0.001$). The 5-year overall survival of the patients with stages I (79.8%) and II (39.7%) tumors were also significantly longer than that of the patients with stages III/IV (16.2%) tumors (Fig. 6, stages I vs III/IV, $P < 0$ .001 and stages II vs III/IV, $P = 0.012$). However, other factors including age, gender, tumor location, and tumor length (≤ 5 cm vs > 5 cm) were not associated with the prognosis. As those cases that received chemoradiotherapy were in more advanced stages, their prognosis was still worse than patients who did not reveive chemoradiotherapy even after such treatment (chemotherapy, $P = 0.042$, and radiotherapy, $P = 0.010$, respectively). In multivariate analysis, which included tumor types and pathological T, N, and TNM stages as entry factors, the TNM stage (hazard ratio, 2.708; 95% confidence interval, 1.786–4.105, $P < 0.001$) was found to be an independent prognostic factor.

Compared with 1852 patients with typical SCC who received esophagectomy in the same period, the MST and 5-year OS of the entire SpCC group were 43 months and 44.8%, respectively,

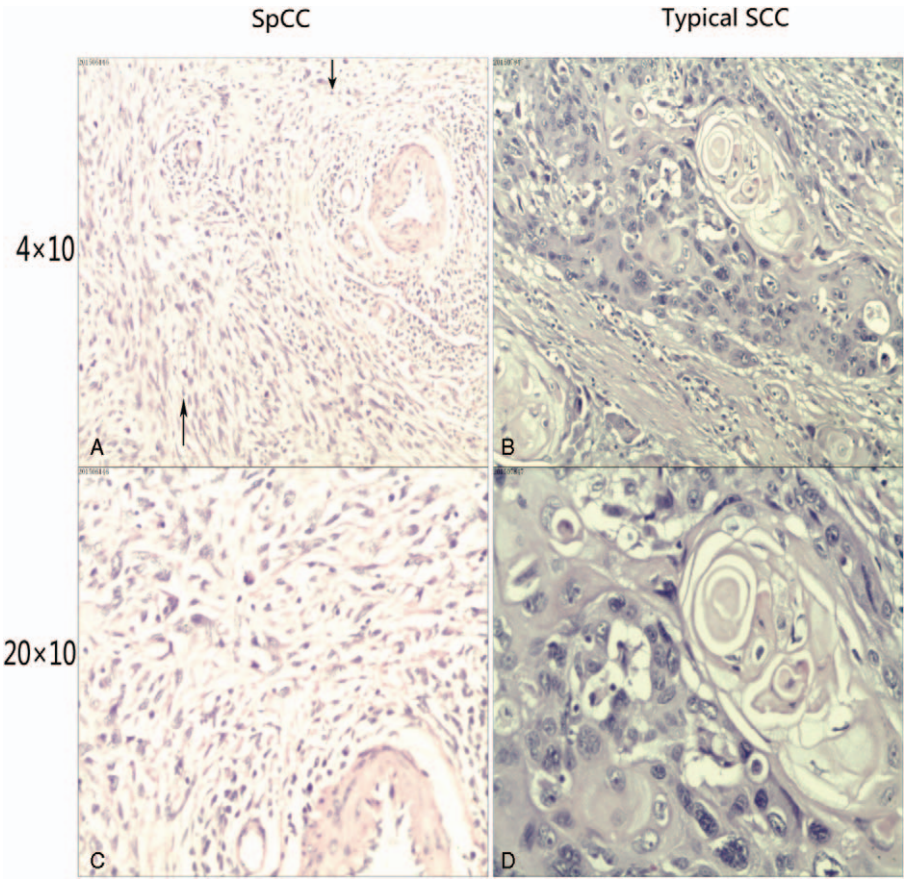

Figure 1. Microscopical comparison between spindle cell carcinoma (A, C) and typical squamous cell carcinoma (B, D) of the esophagus (4 × 10 and 20 × 10 magnification). SpCC is shown to have a malignant sarcomatoid component (A↓) and a squamous cell carcinoma component (A↑). SpCC = spindle cell carcinoma of the esophagus.

which was higher than 37.5 months and 38.3%, respectively, for the typical SCC group ($P = 0.044$, Fig. 7). However, when the data were stratified according to the pathological stages, the survival differences between the SpCC and typical SCC groups disappeared (Table 3). Only in patients with pathological T1/2, the 5-year OS of the SpCC group showed the tendency to be longer than that of the typical SCC group (51.8% vs 45.6%, $P = 0.054$). In patients without lymph node metastasis, the long-term survival was longer in the SpCC group than in the typical SCC group (65.8% vs 49.0%, $P = 0.011$, Fig. 8). Further analysis revealed that in the patients without lymph node metastasis, the percentage of T1/2 with negative lymph nodes in the SpCC group was higher than in the typical SCC group (28/39, 71.8% vs 346/955, 36.2%, $P < 0.001$).

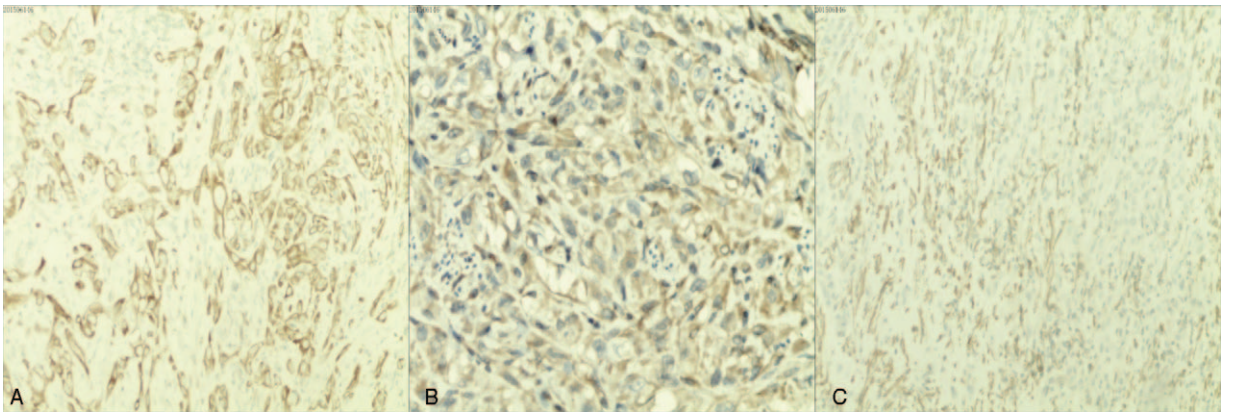

Figure 2. Immunohistochemical staining shows the positive staining of Cytokeratin (A), Vimentin (B), as well as the negative staining of Smooth Muscle Antigen (C) in SpCC. SpCC = spindle cell carcinoma of the esophagus.

Table 2

Univariate analysis of the prognosis for 71 patients with SpCC.

	No. of patients	1-year OS	3-year OS	5-year OS	*P*
Age, y					
<60	43	81.1%	54.1%	46.4%	
≥60	28	81.5%	54.3%	42.3%	0.581
Gender					
Male	59	77.3%	48.5%	42.8%	
Female	12	90.9%	81.8%	54.5%	0.135
Tumor location					
Upper-third esophagus	13	92.3%	75.5%	67.1%	
Mid-third esophagus	38	78.4%	50.4%	41.5%	
Lower third esophagus	20	79.2%	47.5%	36.2%	0.123
Tumor length					
≤5 cm	37	86.5%	61.6%	52.9%	
>5 cm	34	75.2%	45.8%	35.2%	0.081
Pathological T stage					
T1/2	48	93.6%	63.2%	51.8%	
T3/4	23	54.2%	34.5%	29.6%	0.002
Macroscopical type					
Polypoid type	47	93.4%	66.1%	51.7%	
Infiltrative type	24	56.9%	30.6%	30.6%	0.001
Pathological N stage					
N-	39	87.1%	71.3%	65.8%	
N+	32	73.7%	31.8%	17.7%	<0.001
Pathological TNM stage					
Stage I	24	95.8%	83.3%	78.9%	
Stage II	20	84.7%	51.1%	39.7%	
Stage III/IV	27	64.6%	28.3%	16.2%	<0.001
Adjuvant radiotherapy					
No	58	82.3%	59.9%	52.1%	
Yes	13	76.9%	30.8%	15.4%	0.010
Adjuvant chemotherapy					
No	56	81.6%	58.4%	52.2%	
Yes	15	80.0%	40.0%	20.0%	0.042

OS = overall survival, SpCC = spindle cell carcinoma of the esophagus, TNM = tumor-node-metastasis.

3.4. Failure patterns

At the end of the follow-up, 36 patients died of tumor recurrence. The first failure sites found in these cases included distant hematogenous metastases in 16 cases and lymph node recurrences in 18 cases. The hematogenous spread usually occurred in the lung (6 cases), liver (5 cases), bone (4 cases), and adrenal (1 case). Lymph node recurrences often appeared in the cervical or supraclavical lymph nodes (12 cases), mediastinal lymph nodes (7 cases), and upper abdominal lymph nodes (4 cases). Another 3

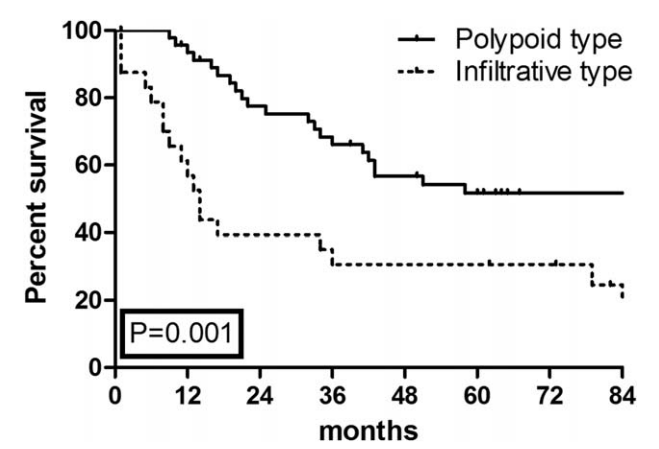

Figure 3. Overall survival in SpCC patients with polypoid tumors (n = 47) is longer than those with infiltrative tumors (n = 24) (*P* = 0.001). SpCC = spindle cell carcinoma of the esophagus.

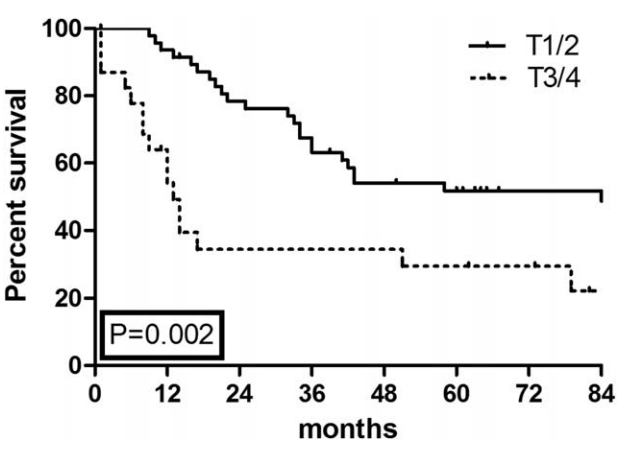

Figure 4. Overall survival for SpCC patients with T1/2 tumors (n = 48) is better than those with T3/4 tumors (n = 23) (*P* = 0.002). SpCC = spindle cell carcinoma of the esophagus.

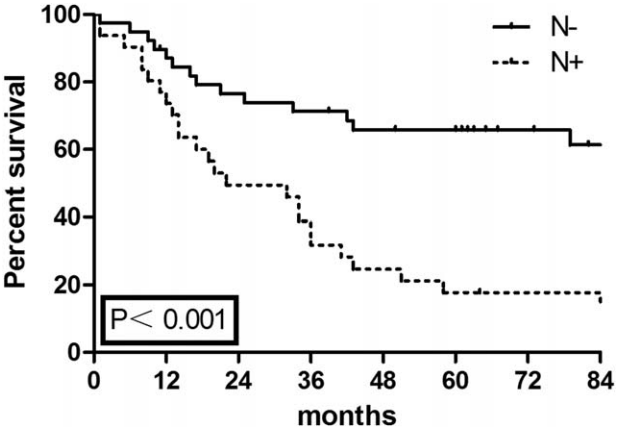

Figure 5. Survival of SpCC patients without locoregional lymph node metastasis (n=39) is longer than those with lymph node metastasis (n=32) ($P<0.001$). SpCC=spindle cell carcinoma of the esophagus.

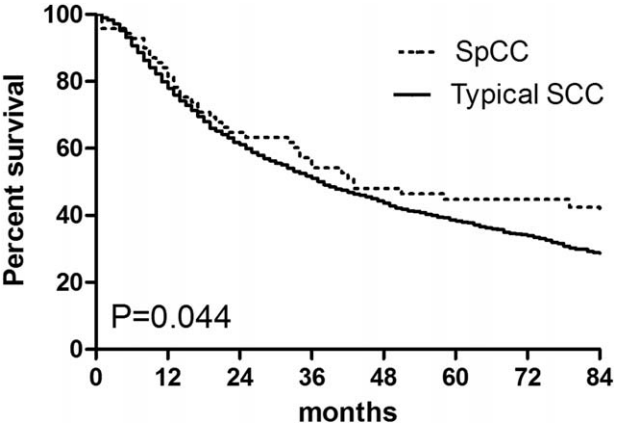

Figure 7. Compared with 1852 patients with typical SCC who received esophagectomy in the same period, the survival rates of the SpCC patients are higher ($P=0.044$). SCC=squamous cell carcinoma, SpCC=spindle cell carcinoma of the esophagus.

cases had anastomotic or gastric remnant recurrence. Metastases to>1 location at the same time were observed in 6 patients.

4. Discussion

The present study has provided a systematic evaluation of the clinical characteristics and treatment outcomes of esophageal SpCC based on a retrospective multicenter analysis of 71 cases, which is the largest series from China. This study confirms the rarity of esophageal SpCC, demonstrating an incidence of 0.63% in all esophageal tumors. The results show that SpCC mostly presents as a polypoid appearance, and the probability of making a correct diagnosis in the early stage is higher. Thus, the long-term survival of SpCC is better than that of typical SCC. However, a greater proportion of SpCC patients (67.6%) is in the stage T1/2 at initial diagnosis and shows a higher tendency toward locoregional lymphatic spread, indicating a highly malignant potential and a necessity of extensive lymphadenectomy in curative esophagectomy.

Histopathologically, the microscopic features of SpCC include 2 components: a sarcomatous component and a carcinomatous component.[2,11,13] The latter component usually consists of malignant SCC, but adenocarcinoma or neuroendocrine carcinoma was also observed in 4 cases in the present study, which was occasionally reported in previous studies.[1,6,16–18] Because of the typical polypoid appearance with large pedunculated masses in the esophageal lumen, obstructive symptoms may occur in the early stages. In the present study, 66.2% of all SpCCs were polypoid types, and the duration of symptoms was shorter than 3 months in most of the patients (81.7%). In accordance with the previous reports,[1,11,19,20] most of the SpCC patients (67.6%) were in stage T1/2 at initial diagnosis, but only 29.7% for typical SCC were T1/2 ($P<0.001$), suggesting that SpCC was more likely to be diagnosed at an early stage. However, as reported,[1,11,19] no significant difference was found in harboring lymph node metastasis between both the groups even at stage T1/2 (41.7% vs 37.1%). This indicates that SpCC tends not to infiltrate deeply into the esophageal wall, but it presents a highly aggressive tendency of lymphatic spread even at the early T stage.

Because of the rarity of SpCC and the absence of consensus on its histological diagnosis and nomenclature in the literature, no standard therapeutic modalities specific to the disease have been determined yet. As previously reported,[9,11,15] surgery was the mainstay of treatment in the present study, and several reasons were identified for the recommendation of surgical therapy. First, a definite diagnosis of SpCC could be hardly made before treatment (14.1%), whereas surgery could help make a definitive diagnosis and provide a chance for cure. Second, locoregional lymphatic metastases were detected in 45.1% of SpCC patients, consistent with the rate of 33% to 65% in former studies,[1,2,7,9,11,14,19,20] suggesting the highly aggressive behavior of the disease. Thus, 2- or 3-field lymphadenectomy should be performed to improve the surgical radicality in esophageal SpCC. Third, Handra-Luca et al[1] reported that high-grade hyperplasia or carcinoma in situ was detected in adjacent esophageal mucosa at a certain distance from the tumor body in 88.2% of all patients, whereas the percentage is 43.7% in the present study. Two of these patients even had extensive carcinoma in situ that spread to the mucosal resection margins, which had never been reported before. Although long-term survivals could also be achieved in single cases that underwent local excision or endoscopic resection,[2,21] more pieces of evidence support that

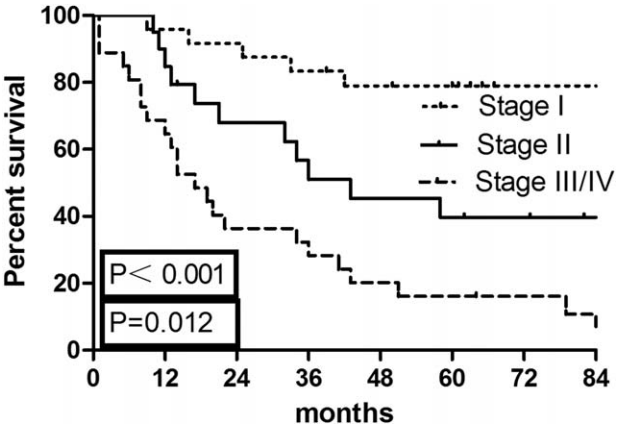

Figure 6. The 5-year OS of the patients with stages I (n=24) (79.8%) and II (n=20) (39.7%) tumors are also significantly longer than that of the patients with stages III/IV (n=27)(16.2%) tumors (stages I vs III/IV, $P<0.001$ and stages II vs III/IV, $P=0.012$). SpCC=spindle cell carcinoma of the esophagus.

Table 3

Comparison of the survival between SpCC and typical SCC based on tumor stage.

	No. of patients	1-year OS	3-year OS	5-year OS	*P*
TNM stage I					
SpCC	24	95.8%	83.3%	78.9%	
SCC	149	96.6%	84.4%	65.5%	0.327
TNM stage II					
SpCC	20	84.7%	51.1%	39.7%	
SCC	853	84.9%	62.0%	48.8%	0.920
TNM stage III/IV					
SpCC	27	64.6%	28.3%	16.2%	
SCC	850	68.8%	34.7%	23.1%	0.342
Pathological T1/2					
SpCC	48	93.6%	63.2%	51.8%	
SCC	550	86.2%	60.2%	45.6%	0.054
Pathological T3/4					
SpCC	23	54.2%	34.5%	29.6%	
SCC	1302	75.2%	47.4%	35.0%	0.210
Pathological N-					
SpCC	39	87.1%	71.3%	65.8%	
SCC	955	83.8%	62.1%	49.0%	0.011
Pathological N+					
SpCC	32	73.7%	31.8%	17.7%	
SCC	897	72.8%	39.7%	27.2%	0.774

OS = overall survival, SCC = squamous cell carcinoma, SpCC = spindle cell carcinoma of the esophagus, TNM = tumor-node-metastasis.

local excision alone may be insufficient for radical therapy and a wide esophagectomy should be considered. Finally, the long-term survival of SpCC is better than that of typical SCC after curative resection in the present study, especially in patients with T1/2 and N0 diseases, suggesting the disease is amenable to surgical treatment. Therefore, the authors recommended that esophagectomy in combination with extended lymphadenectomy should be considered as the primary treatment of choice for the early stage SpCC.

Lymphatic metastasis is the most frequent failure pattern in this group of SpCC, whereas hematogenous metastasis was more frequent in Iyomasa's report,[11] indicating the highly metastatic potential of the malignancy. No survival improvements were observed in this study, as those cases that received chemoradiotherapy were in more advanced stages. But previous studies on typical esophageal SCC have demonstrated that adjuvant chemoradiotherapy may decrease locoregional recurrence and improve the long-term survival.[22–24] Prior studies on SpCC located in other sites have found that chemotherapy and radiotherapy might help improve the prognosis after surgery.[25–28] Although several studies[19,20] have even reported a frustrating result in esophageal SpCC receiving chemoradiotherapy, acceptable treatment responses could still be achieved in individual cases.[15,20,29] Therefore, chemoradiotherapy might be considered in treating SpCC patients with unresectable and recurrent lesions or with lymph node metastasis after surgery because of its early spreading. However, more observations are needed to demonstrate whether chemoradiotherapy is of value in extending patients' life.

Previous reports of esophageal SpCC were too limited in sample size to identify the prognostic factors of the disease. Several recent reports demonstrated that the prognosis of SpCC is comparable to that of typical SCC.[2,9,11,15] The present study revealed that the long-term survival of esophageal SpCC was better than that of typical SCC, as more patients in the former group were in earlier stages. As expected, the macroscopical type and pathological T, N, and TNM stages had a statistically significant impact on the outcome of patients. The survival of polypoid type was better than that of the infiltrative type, but further analysis found that the infiltrative tumors had more lesions in stage T3/4, which was consistent with the results published by Handra-Luca et al[1] and Iyomasa et al.[11] However, in multivariate analysis, only the TNM stage was identified as an independent prognostic factor in this study. Patients in stage I or II at the time of diagnosis had a much more favorable prognosis compared with stages III/IV. This data support that advanced SpCC seems to be more aggressive, and its clinical management should be distinct from SpCC in the early stage.

Despite providing important features of a rare malignancy, based on one of the largest series of esophageal SpCC, certain

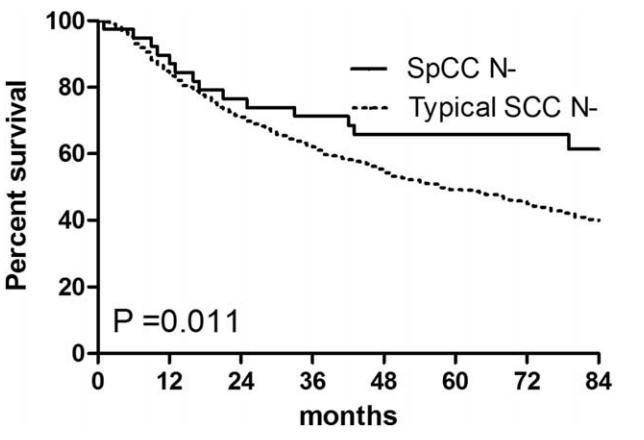

Figure 8. In patients without lymph node metastasis (N-), the long-term survival of SpCC patients (n = 39) is longer than those of typical SCC patients (n = 955) (*P* = 0.011). SCC = squamous cell carcinoma, SpCC = spindle cell carcinoma of the esophagus.

limitations still exist in this study. As a retrospective analysis, no detailed information about recurrence and following therapy was provided, which would be valuable in further analysis. Furthermore, as only 14.1% of SpCC could be diagnosed via biopsy, cases may have been misclassified in patients not undergoing surgical procedures. However, because of the rarity of SpCC, the sample size was too limited in a single center. But a multicenter analysis may lead to possible bias related to the differences in diagnostic and treatment strategies.

In summary, this research focused exclusively on the clinical characteristics and treatment outcomes of the disease. SpCC is an unusual occurrence that can be diagnosed in the early stage. Despite its aggressive histological characteristics, esophagectomy with extended 2- or 3-field lymphadenectomy may achieve definitive treatment in the early stage of this disease, whereas the value of chemoradiotherapy requires further evaluation. The prognosis of SpCC is better than typical SCC after curative therapy.

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